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Re: Our Docket: 500862002300
Patent Application No. 09/657,276
Group Art Unit: 1619

Pursuant to your request attached are the pending claims for Patent Application Nos. 09/424,571 and 09/530,891.

NOVEL CONJUGATE OF RGD-CONTAINING PEPTIDES AND ENDOGENOUS CARRIERS
By Dominique BRIDON et al.
U.S. Serial No. 09/530,891
Client Ref. REDC-800 USA
MoFo Ref. 50086-20008.00

Claims 1-12 are cancelled.

13. (Amended) The method of claim 22, wherein said blood component is a protein.

14. (Amended) The method of claim 22, wherein said reactive entity reacts with an amino group, a carboxyl group, or a thiol group on said blood component.

15. (Amended) The method of claim 22, wherein the reactive entity comprises a N-hydroxysuccinimido-, N-hydroxysulfosuccinimido-, or a maleimido-containing group.

16. (Amended) The method of claim 22, wherein said blood component comprises albumin, immunoglobulin, or combinations thereof.

17. (Amended) The method of claim 22, wherein said derivative is administered intravascularly.

18. (Amended) The method of claim 22, wherein said blood component is albumin.

Claim 19 is cancelled.

20. (Amended) The method of claim 22, wherein said reactive entity is a maleimide group.

21. (Amended) The method of claim 22, wherein said RGD peptide derivative comprises RIARGDFPDDRK.

22. (New) A method for inhibiting cellular adhesion in a patient, comprising administering to the patient an effective amount of a RGD peptide derivative that covalently bonds *in vivo* to a blood component, the RGD peptide derivative comprising a reactive entity coupled to a RGD peptide, the reactive entity reacting *in vivo* with a functionality on the blood component to form the covalent bond, the RGD derivative having an *in vivo* half-life greater than the *in vivo* half-life of the RGD peptide.

23. (New) The method of claim 21 wherein the RGD peptide derivative is selected from the group consisting of Ac-RIARGDFPDDRK(GMBA)-NH_2, Ac-RIARGDFPDDRK(EGS)-NH_2 and MPA-AEA_3RIARGDFPDDRK-NH_2.

We Claim:

1. A local delivery agent comprising a compound of the formula:

X-Y-Z

wherein X is selected from the group consisting of wound healing agents, antibiotics, anti-inflammatories, antioxidants, antiproliferatives, immunosuppressants, anti-infective and anti-cancer agents;

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith.

2. The composition of claim 1 wherein said fixed blood component is a protein.

3. The composition of claim 1 wherein said reactive functionality is selected from the group consisting of an amino group, a carboxyl group or a thiol group.

4. The composition of claim 1 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

5. The composition of claim 5 wherein Z is N-hydroxysuccinimide.

6. The composition of claim 1 wherein X is a peptide.

7. The composition of claim 1 wherein X is an organic molecule.

8. The composition of claim 1 wherein X contains a radioactive isotope.

9. A local delivery agent comprising a compound of the formula:

X-Y-Z

wherein X is selected from the group consisting of wound healing agents, anti-inflammatories, antiproliferatives, and chemotherapeutic agents;

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith.

10. The composition of claim 9 wherein said fixed blood component is a protein.

11. The composition of claim 9 wherein said reactive functionality is selected from the group consisting of an amino group, a carboxyl group or a thiol group.

12. The compositi n f claim 9 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy sulfosuccinimide, maleimide-benzoyl-succinimid , gamma-maleimido-butyryl xy succinimide ester, maleimidopropionic acid, isocyanat ,

thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

13. The composition of claim 9 wherein Z is N-hydroxysuccinimide.

14. The composition of claim 9 wherein X is a peptide.

15. The composition of claim 9 wherein X is an organic molecule.

16. The composition of claim 9 wherein X is a radiolabeled element.

17. A wound healing agent comprising a compound of the formula:

X-Y-Z

wherein X is a therapeutic agent that has wound healing properties;

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith.

18. The composition of claim 17 wherein said fixed blood component is a protein.

19. The composition of claim 17 wherein said reactive functionality is selected from the group consisting of an amin group, a carboxyl group or a thiol group.

20. The composition of claim 17 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

21. The composition of claim 17 wherein Z is N-hydroxysuccinimide.

22. A wound healing agent comprising a compound of the formula:

X-Y-Z

wherein X is an RGD containing peptide have wound healing properties;

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith.

23. The composition of claim 22 wherein said fixed blood component is a protein.

24. The composition of claim 22 wherein said reactive functionality is selected from the group consisting of an amino group, a carb xyl group or a thiol group.

25. The composition of claim 22 wherein Z is selected from the group c nsisting f N-hydroxysuccinimid , N-hydroxy

sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, N-hydroxysuccinimide, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

26. The composition of claim 22 wherein Z is N-hydroxysuccinimide.

27. The composition of claim 22 wherein the RGD containing peptide is:

Ac-RIARGDFPDDRK(EGS)-NH2

where EGS is ethylene glycol-bis(succinimidylsuccinate)

28. A local delivery agent comprising a compound of the formula:

X-Y-Z

wherein X is an anti-restenosis, antiproliferative or an antiangiogenic agent wherein said agent is radioactive, wherein

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on a fixed blood component to form covalent bonds therewith.

29. The composition of claim 28 wherein said fixed blood component is a protein.

30. The composition of claim 28 wherein said reactive functionality is selected from the group consisting of an amin group, a carboxyl group or a thiol group.

31. The composition of claim 28 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

32. The composition of claim 28 wherein Z is N-hydroxysuccinimide.

33. A local delivery agent comprising a compound of the formula:

X-Y-Z

wherein X is an anti-restenosis, an antiproliferative or an antiangiogenic agent wherein said agent contains an RGD peptide

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith.

34. The composition of claim 33 wherein said fixed blood component is a protein.

35. The composition of claim 33 wherein said reactive functionality is selected from the group consisting of an amino group, a carboxyl group or a thiol group.

36. The composition of claim 33 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy

sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

37. The composition of claim 33 wherein Z is N-hydroxysuccinimide.

38. The composition of claim 33 wherein the RGD peptide is:

Ac-RIARGDFPDDRK(EGS)-NH2

wherein EGS is ethylene glycol-bis(succinimidylsuccinate) and Ac is an acetylated terminal amino acid.

39. A local delivery agent comprising a compound of the formula:

X-Y-Z

wherein X is an anti-restenosis, an antiproliferative or an antiangiogenic agent wherein said agent includes a radioactive isotope, wherein

Y is a linking group consisting of 0-30 atoms; and

Z is a chemically reactive entity capable of reaction with a reactive functionality on a fixed blood component to form covalent bonds therewith.

40. The composition of claim 39 wherein said fixed blood component is a protein.

41. The composition of claim 39 wherein said reactive

functionality is selected from the group consisting of an amino group, a carboxyl group or a thiol group.

42. The composition of claim 39 wherein Z is selected from the group consisting of N-hydroxysuccinimide, N-hydroxy sulfosuccinimide, maleimide-benzoyl-succinimide, gamma-maleimido-butyryloxy succinimide ester, maleimidopropionic acid, isocyanate, thiolester, thionocarboxylic acid ester, imino ester, carbodiimide anhydride and carbonate ester.

43. The composition of claim 39 wherein Z is N-hydroxysuccinimide.

44. The composition of claim 39 wherein said radioactive isotope is a beta ray or a gamma ray emitter.

45. A method of increasing the retention time of a therapeutic agent locally administered to a site, comprising:

delivering to a localized site in a mammal a compound according to claim 3 of the formula:

X-Y-Z

wherein:

X is a therapeutic agent selected from the group consisting of wound healing agents, antibiotics, anti-inflammatories, antioxidants and chemotherapeutic agents;

Y is a linking group of 0-30 atoms; and

Z is a chemically reactiv group capable of reaction with a reactive functionality of said site to f rm one or more covalent bonds therewith.

46. The method of claim 32 wherein said device is selected from the group consisting of syringes, catheters, trocars and endoscopes.

47. The method of claim 32 wherein said formulation is delivered intravascularly.

48. The method of claim 33 wherein said formulation is delivered topically.

49. The method of claim 33 wherein said formulation is delivered intraarterially.

50. The method of claim 45 wherein said mammal is a human.

51. A method of promoting wound healing at a wound site, comprising:

applying a compound of the formula X-Y-Z wherein X is a wound healing agent, Y is a linking group between 0-30 atoms and Z is a chemically reactive entity capable of reaction with a reactive functionality on fixed blood components to form covalent bonds therewith, wherein said compound is applied at or near said site to permit covalent bond formation of said compound to a reactive functionality near said site.

52. A method of treating a tumor, comprising:

applying a compound of the formula X-Y-Z wherein X is an anti-cancer agent, Y is a linking group between 0-30 atoms and Z is a chemically reactive entity capable of reaction with a reactive

functionality on fixed blood components to form covalent bonds therewith, wherein said compound is applied at or near said tumor to permit covalent bond formation of said compound to a reactive functionality at or near said tumor.